



A step forward to the era of immunotherapy in resectable esophageal cancer: 2021 NCC/CATS/CSTCVS/STM expert consensus on perioperative immunotherapy for esophageal cancer

Ka-On Lam^{1^}, Lok-Yee Hiok¹, Simon Law^{2^}

¹Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China; ²Department of Surgery, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China

Correspondence to: Ka-On Lam. Department of Clinical Oncology, LKS Faculty of Medicine, The University of Hong Kong, Hong Kong, China. Email: lamkaon@hku.hk.

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Esophageal cancer is prevalent in the Asian population and is notorious for being highly lethal in both locally advanced and metastatic settings. With the advancement in multimodal perioperative therapy, the overall survival (OS) after esophagectomy has been improved remarkably. Neoadjuvant chemoradiation is practiced worldwide as a standard of care that increases pathologic complete response (pCR) rate and improves OS (1). Nevertheless, the disease recurrence rate is still substantial. Immune checkpoint inhibitors (ICIs) have shown promising efficacy in the adjuvant and palliative settings in several landmark phase III randomized controlled studies including the CheckMate 577 study (2), the KEYNOTE-590 study (3), the CheckMate 649 study (4), the ATTRACTION-4 study (5), and the recently published CheckMate 648 study (6). It is therefore potentially very advantageous to boost the chance of cure for esophageal cancer by adding ICIs in the perioperative settings.

This editorial highlights the recent Consensus jointly developed by the National Cancer Center (NCC), Chinese Association of Thoracic Surgeons (CATS), Chinese Society for Thoracic and Cardiovascular Surgery (CSTCVS), and Esophageal Disease Panelists of Society for Translational

Medicine (STM) (7). In the absence of robust phase III data, a recent cross-sectional survey, as quoted in the introduction of the Consensus, has already reported an astonishing rate (82.6%) of perioperative immunotherapy combined with chemoradiation or chemotherapy being implemented in the 69 major centers for esophageal cancer in China. It is understood that most of the implementations are within clinical trial settings, but the proliferating trend implicates an unmet need to make the current Consensus timely and highly anticipated. The group is to be congratulated for the effort in bringing together a panel of world-renowned experts in esophageal cancer and arrived at recommendations with the modified Delphi method and GRADE approach (8,9).

The Consensus contains 11 recommendations which are based on variable qualities of evidence and levels of consensus among the experts. Recommendation 1 states that preoperative immunotherapy should be limited to the framework of clinical trials because of insufficient evidence (quality of evidence: medium; consensus level: 100%). This is a modest, yet practical, recommendation to avoid too liberal use of immunotherapy preoperatively in the real world. Although studies like the PALACE1 (10)

[^] ORCID: Ka-On Lam, 0000-0002-7523-5088; Simon Law, 0000-0002-6518-5806.

Table 1 Summary of ongoing trials of perioperative immunotherapy for esophageal cancer globally

Trial	Est. year of completion	Country	Histology	Design	Intervention	Patients	Primary outcomes
INEC-study, [NCT03544736]	2025	Norway	SCC/AC	Three parallel cohort, multicenter, open-label, phase I/II	Palliative RT + nivolumab; definitive CRT + nivolumab; nCRT + nivolumab then S	N=30	Tolerability (incidence of AE according to CTCAE 5.0)
Study of anti-PD-L1 in combination with chemo(radio)therapy for oesophageal cancer, [NCT02735239]	2022	UK	SCC/AC	Safety run-in phase I (cohorts A1 and A2) and an expansion phase II (cohorts B, C, C-FLOT, D)	Durvalumab before CT (oxaliplatin + capecitabine); durvalumab + tremelimumab; durvalumab + CT + S; durvalumab + CRT + S; durvalumab + C-FLOT + S	N=75	Dose-limiting toxicity, AE, change in baseline in laboratory evaluation
ICONIC trial, [NCT03399071]	2021	UK	GEA	Single center, single arm, phase II	Avelumab + FLOT + S	N=40	MAD pCR aimed at >25%
Pilot study of perioperative CT + immunotherapy followed by surgery in localized esophageal & GEA, [NCT03784326]	2021	USA	GEA	Early phase I	Atezolizumab + oxaliplatin and fluorouracil + S	N=30	pCR

INEC-stay, Safety and Feasibility of Irradiation and Nivolumab in Esophageal Cancer; SCC, squamous cell carcinoma; AC, adenocarcinoma; RT, radiotherapy; CRT, chemoradiotherapy; nCRT, neoadjuvant chemoradiotherapy; S, surgery; AE, adverse events; FLOT, fluorouracil + leucovorin + oxaliplatin + docetaxel; CT, chemotherapy; ICONIC trial, the peri-operative immuno-chemotherapy in operable oesophageal and gastric cancer; GEA, gastroesophageal adenocarcinoma; MAD, maximum administered dose; pCR, pathologic complete response.

and the PERFECT study (11) have shown an early signal of feasibility, further larger scale prospective studies are warranted for not only the efficacy/safety data but the mechanistic rationale of the optimal regimen. *Tables 1,2* summarize the ongoing global and China studies, respectively. Recommendation 4 suggests that when neoadjuvant immunotherapy is being considered, 2–4 cycles of immunotherapy with chemotherapy or chemoradiation are recommended (quality of evidence: low; consensus level: 91.9%). However, for whom and when neoadjuvant immunotherapy should be considered remains ambiguous with this recommendation. Regarding the question for “whom”, it is assumed that those with bulky tumor or significant nodal burden are potential candidates but whether adding immunotherapy could lead to significant downstaging or not, in the specified time window, is still uncertain. Concerning “when”, vast data on immunotherapy in gastroesophageal cancer suggests that the median time to response is around 6–10 weeks and late-responders are also seen (3-6). So, the jury is still out for the optimal number of cycles and the picture is even more complicated if postoperative immunotherapy is to be added.

As expected, the highest quality of evidence and level of consensus is that surgery remains the standard of care regardless of the modality that patients are treated preoperatively. According to recommendations 7 and 8, esophagectomy performed in either open or minimally invasive method with 2- or 3-field lymph node dissection (depending on the tumor site and supraclavicular lymph node involvement) should be the first-line approach in all esophageal cancer patients after neoadjuvant immunotherapy (quality of evidence: high; consensus level: 97.3%). Following preoperative immunotherapy, the transthoracic and transabdominal surgical approaches are recommended for patients with Siewert type I and III esophagogastric junction tumors respectively. and for Siewert type II cancer it should be decided by thoracic or gastrointestinal surgeons (quality of evidence: high; consensus level: 94.6%). Notably, most experts in the panel believe that preoperative immunotherapy would not significantly add to surgical morbidity and mortality. Perhaps this should be heeded with caution, especially in the setting of immunotherapy combination with chemoradiation. Lee and associates reported a single-

Table 2 Summary of ongoing trials of neoadjuvant immunotherapy for esophageal cancer in China

Trial	Est. year of completion	Histology	Design	Regimen	Patients	Outcomes
CRISEC, [NCT04776590]	2023	SCC	Single arm, phase II	RT: PTV 41.4 Gy in 23 fractions, 5 days per week; CT: paclitaxel (albumin bound) (100 mg/m ³ of BSA weekly) and carboplatin (AUC of 2 mg/mL/min weekly) for 5 weeks, concurrent with RT; immunotherapy: tislelizumab (200 mg per 3 weeks)	N=30	pCR, OS, DFS
Neoadjuvant treatment modalities for esophageal cancer, [NCT04821843]	2025	SCC/AC	Parallel assignment cohort stud, phase III	nCT: paclitaxel based q1–3W/5-FU analog based; W1–5 qW or d1–14, q3W according to physician's preference +/- immunotherapy; nCRT: RT: 40–50 Gy/1.8–2.2 Gy/20–25 fractions +/- immunotherapy: nimotuzumab 200–400 mg, d1, qW then S: radical esophagectomy	N=2,000	OS, PFS, pCR, acute and late toxicities (NCI-CTC version 5.0)
The exploration of immunodynamic monitoring in the population evaluation of nCT immunotherapy in patients with solid tumor of the chest, [NCT05044728]	2022	SCC	Prospective, single-arm, open cohort study (randomly stratified within the group)	Stratifies 1:1 to receive anti-PD-1 antibody (240 mg, every 3 weeks for total 2 cycles) in group A: 24 hours after the end of CT (paclitaxel and carboplatin) or group B: on the first day of each cycle, CT will be 24 hours after the end of immunotherapy. paclitaxel, 135 mg/m ² , IV, d1, q3W, for total 2 cycles; Carboplatin, AUC =5 (according to Calvert formula), IV, d1, every 3 weeks for a total of 2 cycles	N=80	ORR, pCR, irAEs, Functional subsets of peripheral CD8 positive T cells
A real-world study evaluating the efficacy and safety of immune checkpoint inhibitors and CT for advanced esophageal cancer, [NCT04822103]	2021	SCC	Retrospective study	NA	N=150	ORR, pCR
The safety and efficacy of camrelizumab in combination with RT for neoadjuvant esophageal, squamous cell carcinoma, [NCT05176002]	2023	SCC	Phase I: (12 cases, with at least 5 achieving efficacy); phase II: if 14 cases were effective, cases >13	All patients receive radical surgery within 4–8 weeks after completion of neoadjuvant camrelizumab in combination with standard RT	N=26	Major/complete pathological remission rate, number and percentage of cases of all AEs

CRISEC, chemoradiotherapy plus immunotherapy followed by surgery for esophageal cancer; SCC, squamous cell carcinoma; RT, radiotherapy; PTV, planning target volume; CT, chemotherapy; BSA, body surface area; nCRT, neoadjuvant chemoradiotherapy; PFS, progression-free survival; AUC, area under the curve; pCR, pathologic complete response; OS, overall survival; DFS, disease-free survival; AC, adenocarcinoma; nCT, neoadjuvant chemotherapy; S, surgery; ORR, overall response rate (RECIST v1.1); irAEs, immune-related adverse events; NA, not available; AEs, adverse events.

arm phase II study that added pembrolizumab concurrent with preoperative chemoradiation (12). While the pCR rate reached 46.1%, there were two postoperative deaths primarily attributed to acute lung injury. Without further safety data from well-designed prospective studies, acute lung injury as a potential sequela of concurrent radiotherapy and immunotherapy should always be assumed until proven otherwise. This is particularly true in Asia where thoracic esophageal squamous cell carcinoma is predominant and the radiotherapy field encompasses a substantial volume of lung parenchyma.

A predictive biomarker is a holy grail for immunotherapy to guide proper patient selection and maximize therapeutic ratio. Recommendation 3 suggests that programmed cell death-ligand 1 (PD-L1) expression, as measured by combined positivity score (CPS) may be helpful in decision making (quality of evidence: low; consensus level: 75.7%). Microsatellite instability resulting from mutations causing DNA mismatch-repair protein deficiency is a strong predictor of immunotherapy benefit but it is only relevant in less than 1% of patients with esophageal cancer. Alternative biomarkers such as tumor mutational burden (TMB), neurotrophic tyrosine receptor kinase (NTRK), and infiltrating immune cells still require clinical validation. Innovation is all that is required here. The PERFECT-trial suggests that it is promising to explore the IFN- γ signature (11). The AuspiCiOus study from Netherland [NCT05177133] quantifies RNA level and infiltrating immune cells in biopsies, blood, and faeces to determine IFN- γ expression before and during treatment. Moreover, the changes in RNA expression and phenotype of peripheral blood mononuclear cells (PBMCs), expression level of ADAM12 in tumor tissue, the concentration of circulating tumor (ct) DNA in blood, and cytokine/chemokine profile in blood before and during treatment are obtained. This hopefully will provide a very comprehensive panel of markers, including the fecal microbiome, for response prediction and disease monitoring in the future.

If there is anything that the Consensus could be improved, it could stratify for adenocarcinoma and squamous cell carcinoma individually as their tumor biology and response to immunotherapy are different. It is anticipated that a reasonable bulk of evidence specific to squamous cell carcinoma will be available in the coming 2–4 years and most of these will be coming from China (Table 2). Studies in China but not yet recruiting also include “*Neoadjuvant Immunotherapy to ESCC, a phase 2 randomized control trial comparing Sintilimab Injection*

plus Paclitaxel and Cisplatin and Paclitaxel plus Cisplatin combined chemotherapy” [NCT04625543] and is expected to be completed in 2023. “*Neoadjuvant immunotherapy Combined With Chemoradiotherapy Versus Neoadjuvant Chemoradiotherapy for Locally Advanced Esophageal Squamous Cell Carcinoma (cT1b-3N1-2M0, cT3-4aN0M0): A Multi-center Prospective Randomized Clinical Trial also on Tislelizumab*” [NCT04973306] is expected to be completed in 2027. Their results will be valuable in supplementing previous trials such as NICE and KEEP-G 03 (13,14).

In summary, the Consensus is both timely and practical at this point of time when the treatment algorithm for resectable esophageal cancer is rapidly evolving. In light of limited evidence available, especially in the area of neoadjuvant immunotherapy, the Consensus should not be regarded as the definitive answer but instead as a proper framework to steer the academic community in the right direction for good clinical practice and trial design towards the era of immunotherapy in resectable esophageal cancer !

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Footnote

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